

**PROCESS FOR THE PREPARATION OF 1, 4- BENZODIAZEPINE
DERIVATIVES**

Field of the Invention

The field of the invention relates to a process for the preparation of 1,4-
 5 benzodiazepine derivatives. It also relates to pharmaceutical compositions that include the
 1,4-benzodiazepine derivatives.

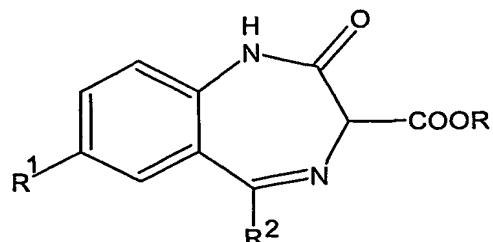
Background of the Invention

1,4 benzodiazepine derivatives such as clorazepate are useful for the treatment of
 anxiety disorders. Several processes have been reported for the preparation of 1,4-
 10 benzodiazepine derivatives, including 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-
 benzodiazepine-3-carboxylic acid i.e. clorazepate, for example, in U.S. Patent Nos.
 3,516,988; 3,657,223; 4,051,127; GB 1117200, EP 22710; and ES 428622.

U.S. Patent No. 3,516,988 discloses a process for the preparation of 1,4 benzodiazepine
 derivatives including ethyl clorazepate, comprising reacting an ortho-aminoarylketimine
 15 with anhydrous lower aliphatic acid or mineral acid. *J. Org. Chem.* 1973, 38, 449-456
 describes the synthesis of ethyl clorazepate by reducing ethyl 2'-benzoyl-4-
 chloromesoxalanilate-2-oxime with zinc dust and acetic acid and further refluxing the
 residue, obtained after workup, in benzene in the presence of acetic acid to obtain ethyl
 clorazepate. It further discloses the synthesis of ethyl 2'-benzoyl-4-chloromesoxalanilate-
 20 2-oxime by nitrosating ethyl 2'-benzoyl-
 4-chloromalonilate with sodium nitrite in acetic acid.

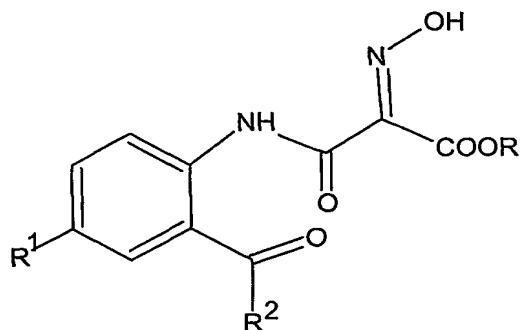
Summary of the Invention

In one general aspect there is provided a process for preparing 1,4 benzodiazepine
 derivatives of formula I in a single step,



Formula I

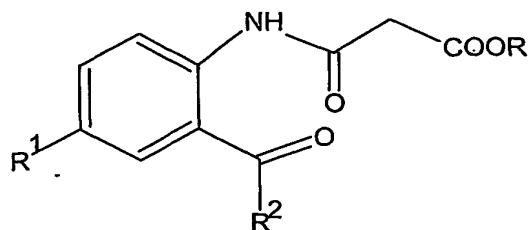
wherein R represents hydrogen, alkyl of C₁-C₅, aryl or arylalkyl; R¹ represents hydrogen, halogen, trifluoromethyl, lower alkyl (C₁-C₄), lower alkoxy(C₁-C₄), nitro or amino groups; and R² represents furyl, thienyl, cyclohexyl, lower alkyl (C₁-C₄) or phenyl, which may be substituted by halogen atom, trifluoromethyl, nitro, lower alkyl (C₁-C₄) or lower alkoxy (C₁-C₄) groups. The process includes reacting an oxime of formula II,



Formula II

wherein R, R¹ and R² are as defined above, with a reducing agent, in the presence 10 of an acid catalyst at a temperature. Thus the reduction of the oxime of formula II, and cyclization to get the compound of formula I are achieved simultaneously in a single step.

In another general aspect there is provided a process for preparing the compound of formula II. The process includes nitrosation of an amide of formula III,



Formula III

15

wherein R, R¹ and R² are as defined above, with sodium nitrite in the presence of a strong inorganic acid.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of a 1,4-benzodiazepine derivative; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The details of one or more embodiments of the inventions are set forth in the 5 description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have developed an efficient process for the preparation of 1,4-benzodiazepine derivatives of formula I in a single step, wherein R represents hydrogen, 10 alkyl of C₁-C₅, aryl or arylalkyl; R¹ represents hydrogen, halogen, trifluoromethyl, lower alkyl(C₁-C₄), lower alkoxy(C₁-C₄), nitro or amino groups; and R² represents furyl, thienyl, cyclohexyl, lower alkyl (C₁-C₄) or phenyl, which may be substituted by halogen atom, trifluoromethyl, nitro, lower alkyl (C₁-C₄) or lower alkoxy (C₁-C₄) groups. The process involves reacting an oxime of formula II, with a reducing agent, in the presence of 15 an acid catalyst, wherein R, R¹ and R² are as defined above.

The term "halogen" includes fluorine, chlorine, bromine, and iodine. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, and tert-butyl groups. In some particular examples, R represents methyl or ethyl, R¹ represents chlorine and R² represents phenyl in the compounds of formula I and II.

20 The reducing agents which can be used for the preparation of compounds of formula I include metal/acids and hydrogenation catalysts. For example, transition metals such as Zn, Fe, and Sn used with acid such as hydrochloric acid, acetic acid and formic acid may be employed as the metal/acid reducing agents.

Examples of hydrogenation catalysts include transition metals or compounds 25 thereof such as Raney nickel and rhodium complexes used in the presence of hydrogen. The reduction may be carried out at normal pressure, or at elevated pressure depending on the choice of catalyst. In particular, it may be carried out at a hydrogen pressure of from about 1-7 Kg/cm².

Examples of acid catalysts include organic and inorganic acids, for example, 30 carboxylic acids such as formic acid, acetic acid and propionic acid and inorganic acids such as hydrochloric acid, hydrobromic acid and mixtures thereof.

The acid used in the metal/acid combination as the reducing agent may also be used as acid catalysts.

The reaction of compound of formula II to obtain the compound of formula I may be carried out in the presence of a suitable solvent. Suitable solvents for the reaction are 5 inert organic solvents that do not change under the reaction conditions. Examples of such solvents include ethers such as diethylether, diisopropylether and dimethoxyethane; alcohols such as methanol, ethanol, isopropanol and butanol; ketones such as acetone and methyl isobutyl ketone; nitriles such as acetonitrile; chlorinated hydrocarbons such as methylene chloride, ethylene dichloride and carbon tetrachloride; esters such as 10 ethylacetate and isopropylacetate; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; cyclic ethers such as dioxane and tetrahydrofuran; and mixtures thereof.

The acid catalysts used in the process may also be used as a solvent. The reaction may be carried out at a temperature range from about 35°C to about 75°C. In particular, it may be carried 15 out at a temperature range from about 45°C to about 65°C. The reaction mixture may be stirred from about 3 to 5 hours depending on the temperature.

The compounds of formula I may be converted to compounds of formula IV, wherein M represents an alkali metal; R¹ represents hydrogen, halogen, trifluoromethyl, lower alkyl (C₁-C₄), lower alkoxy(C₁-C₄), nitro or amino groups; and R² represents furyl, 20 thienyl, cyclohexyl, lower alkyl (C₁-C₄) or phenyl, which may be substituted by halogen atom, trifluoromethyl, nitro, lower alkyl (C₁-C₄) or lower alkoxy (C₁-C₄) groups, by method known in the art such as reacting compounds of formula I with alkali metal hydroxides in the presence of an alcohol. Examples of alkali metal include lithium, sodium and potassium. Examples of alcohol include methanol, ethanol, isopropanol, 25 butanol, and mixtures thereof.

The inventors have also developed a process for the preparation of compound of formula II, wherein R represents hydrogen, alkyl of C₁-C₅, aryl or arylalkyl; R¹ represents hydrogen, halogen, trifluoromethyl, lower alkyl(C₁-C₄), lower alkoxy(C₁-C₄), nitro or amino group; and R² represents furyl, thienyl, cyclohexyl, lower alkyl (C₁-C₄) or phenyl, 30 which may be substituted by halogen atom, trifluoromethyl, nitro, lower alkyl (C₁-C₄) or lower alkoxy(C₁-C₄) group. The process involves nitrosating an amide of formula III, with sodium nitrite in the presence of a strong inorganic acid.

Examples of inorganic acids which can be used in nitrosation of the compound of formula III to obtain the compound of formula II include hydrochloric acid, hydrobromic acid, hydrogenthiocyanide, and mixtures thereof.

The nitrosation reaction to obtain the oxime of formula II is faster in the presence 5 of a strong acid and side reactions or decomposition of the product are minimized. The reaction was found to equilibrate and not go to completion in the presence of a weak acid such as acetic acid.

The nitrosation reaction may be carried out in the presence of a suitable solvent. Suitable solvents for the reaction are inert solvents that do not change under the reaction 10 conditions. Examples of such solvents include ethers such as dimethoxyethane, dioxane and tetrahydrofuran; alcohols such as methanol, ethanol, isopropanol and butanol; chlorinated hydrocarbons such as methylene dichloride and ethylenedichloride; esters such as ethylacetate and isopropylacetate; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; water, and mixtures thereof.

15 The compounds of formula III can be prepared by conventional procedures such as those reported in *J. Org. Chem.* 1973, 38, 449-456.

The present invention is further illustrated by the following examples which are provided to be exemplary of the inventions and is not intended to limit the scope of the invention.

20 Example 1

Preparation of methyl 2'-benzoyl-4-chloromesoxanilate

A solution of sodium nitrite (238g) in water (420 ml) was added slowly to a vigorously stirred suspension of methyl 2' benzoyl-4-chloromalonanilate (140g) in denatured spirit (1400ml) and concentrated hydrochloric acid (700ml). After stirring for 2 hours, the 25 product was isolated by cooling and filtration, and washed with water to remove salts. The wet material was washed with toluene (980 ml) and dried to obtain 126g of the title compound.

(HPLC Purity = 99.31%)

Example 2

30 Preparation of ethyl 2'-benzoyl-4-chloromesoxanilate

A solution of sodium nitrite (228.6g) in water (420 ml) was added slowly to a vigorously stirred suspension of ethyl 2' benzoyl-4-chloromalonanilate (140g) in denatured spirit (1400ml) and concentrated hydrochloric acid (700ml). After stirring for 2 hours, the product was isolated by cooling and filtration, and washed with water to remove salts.

- 5 The wet material was washed with toluene (980 ml) and dried to yield 123g of the title compound.

(HPLC Purity = 99.69%)

Example 3

Preparation of methyl ester of clorazepate

- 10 To acetic acid (1300 ml) were added methyl 2'-benzoyl-4'-chloromesoxalanilate (175g) and activated Raney Nickel (93g) and stirred. Hydrogen pressure (5.0 kg/cm²) was then applied to the reaction mixture and heated to 53 °C. The reaction was continued for 3 to 5 hours at 2 to 5 Kg/cm². After the reaction was over, the reaction mixture was filtered and acetic acid was recovered (about 70%) to give a concentrate. The title product was
15 isolated by cooling the concentrate and filtration of the precipitate obtained. The precipitate so obtained was then washed with water and dried to get 125 g of the product.

(HPLC Purity = 99.26%)

Example 4

Preparation of ethyl clorazepate

- 20 To acetic acid (1300 ml) was added ethyl 2'-benzoyl-4'-chloromesoxalanilate (175g) and activated Raney Nickel (93g) and stirred. Hydrogen pressure (5.0 kg/cm²) was then applied to it and heated to 62 °C. The reaction was continued for 3 to 5 hours at 2 to 5 Kg/cm². After the reaction was over, the reaction mixture was filtered and the solvent was recovered (about 70%) to give a concentrate. The product was isolated by cooling the
25 concentrate and filtration of the precipitate obtained. The precipitate so obtained was then washed with water and dried to get 118.5g of the product.

(HPLC Purity = 99.22%).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.